REMARKS

I. Status of Claims and Formal Matters

Claims 11, 16, 17 – 20, 22 – 26, 28 – 33 are pending in the application. Applicants respectfully reserve the right to pursue any canceled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

II. The Rejections Under 35 U.S.C. § 103 Are Overcome

Claims 11, 16 - 20, 22 – 26, and 33 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Yoji et al (Interaction of Intrathecally Infused Morphone and Lidocaine in Rats (Part I): Synergistic Antinociceptive Effects, *Anesthesiology*, December 1998, vol 89(6), 1455-1463. – "Yoji"), in view of Goodman and Gilman (*The Pharmacological Basis of Therapeutics*, seventh edition, 302-305 and 310-312 – "Goodman"), and in view of Elkhoury *et al.* (USPN 5589480 – "Elkhoury") in further view of Ptchelintsev *et al.* (USPN 5834513 – "Ptchelintsev"). Applicants respectfully disagree and traverse this rejection.

The present invention is directed to methods for providing synergistically effective amounts of morphine and butamben to potentiate analgesia at peripheral sites in a subject.

Yoji teaches the synergistic effects of morphine and lidocaine or bupivicaine when systemically administered via bolus injection or continuous coinfusion. Yoji does not teach the administration of butamben. Similarly, Yoji does not teach the topical administration of these compounds nor does Yoji suggest that the synergistic effect would be retained in the periphery via topical administration.

The synergistic administration of morphine and butamben for providing topical analgesia is alleged to have been prima facie obvious to one of ordinary skill in the art at the time of filing in view of the antinociceptive composition of Yoji, discussed above, in view of the mechanism of action of anesthetics described by Goodman in combination with Elkhoury, which teaches the use of morphine for providing topical analgesia, and Ptchelintsev, which teaches the use of butamben as a topical analgesic. The Examiner alleges that it would have been logical to combine the teaching of these references given that the analgesic properties were each known individually in the art and their synergistic effect would have been expected.

It is respectfully submitted that the topical combination of morphine and butamben in the periphery produces a synergistic result that would have been unexpected to one of skill in the art of pain management at the time that the present application was filed.

To properly determine a prima facie case of obviousness, the Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P § 2142. This is important as "impermissible hindsight must be avoided and the legal conclusion must be gleaned from the prior art." Id. Three basic criteria must then be met: first, there must be some suggestion or motivation to modify or combine the cited references; second, there must be a reasonable expectation of success; and third, the prior art references must teach or suggest all the claim limitations. M.P.E.P §2143. With regard to the first criterion, the "mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." M.P.E.P §2143.01 (*citing In re Mills, 916 F.3d 690* (Fed. Cir. 1990)). "Knowledge in the prior art of every element of a patent claim ... is not of itself sufficient to render claim obvious. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Teleflex, [Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1333-34 (Fed. Cir. 2002)]. The issue is whether substantial evidence supports the judgment (under the clear and convincing evidence standard) that a person having ordinary skill in the art would not have been motivated to replace the [prior art] combination ... with [the claimed combination.]" *Abbott Laboratories v. Syntron Bioresearch, Inc.*, 334 F.3d 1343, (Fed. Cir. 2003).

It is alleged that lidocaine, bupivacaine and butamben all possess the same mechanism of action. Goodman teaches that lidocaine and procaine use the same generally accepted mechanism of action as local anesthetics and that benzocaine, an "ester-type" derivative of procaine, is similar to butamben picrate in its low aqueous solubility. Nevertheless, Goodman also teaches that lidocaine, unlike procaine and benzocaine, is an aminoacetamide (an amide-type anesthetic) and thus will react differently in patients than ester-type anesthetics owing to their different metabolic pathway (hydrolysis via plasma esterase and the liver versus hepatic endoplasmic reticulum). This can be evidenced by increased patient sensitivity and incidence of allergy to ester-type anesthetics. Like lidocaine, bupivacaine is an amide-type anesthetic comprising a butyl piperidine group. Accordingly, lidocaine and bupivacaine, amide-type

anesthetics, and butamben, an ester-type anesthetic, possess different pharmacological properties.

Goodman also teaches that lidocaine, unlike butamben, is a highly soluble anesthetic. Since Yoji is administering its combination via bolus injection or continuous coinfusion, one of skill in the art would lack the motivation to substitute butamben in the combination of Yoji as the solubility of butamben would limit its usefulness intravenously. At most, the proposed combination is "obvious to try," however, it has long been established that this is not the standard of 35 U.S.C. § 103. *In re Geiger,* 815 F.2d 686, 655 (Fed. Cir. 1987).

While both lidocoaine and butamben act as anesthetics, there is no suggestion in the cited art that they are interchangeable, especially if used exclusively in the periphery. Indeed, butamben is an ester-type anesthetic whereas lidocaine is an amide-type anesthetic. As discussed above, while ester-type and amide-type anesthetics generally work via the same mechanism, they utilize different metabolic pathways. As such, even if one were to combine morphine and butamben in the method of Yoji, there would have been no expectation of success, as the synergistic effect may have been prevented by this metabolic pathway. Indeed, Yoji confirms this lack of expectation by concluding that "the nature of interaction may be altered depending on the type of opiod receptor subtype or local anesthetic."

Furthermore, the teachings of Yoji are limited to providing a systemic antinociceptive effect in the central nervous system that cannot be extrapolated to a local antinociceptive effect in the periphery. The potential for peripheral mechanisms to play a significant role in the mediation of antinociceptive responses was unknown prior to the teaching of the present invention. Opiod analgesia was thought to be mediated through the central nervous system (i.e., systemically) rather than through peripheral opiod receptors. Those skilled in the art did not appreciate the significance of peripheral opiod receptor stimulation, much less the significance of combining opiod analgesics and local anesthetics at these peripheral sites.

Finally, there is no motivation to combine Yoji and/or Goodman with Elkhoury and Ptchelintsev. As discussed above, Elkhoury and Ptchelintsev describe the topical administration of morphine and butamben, respectively. While the topical anesthetic properties of each of morphine and butamben are disclosed by these references, there is no expectation of their

synergistic effect in the periphery. Yoji does not rectify this deficiency as the synergistic effect would not be anticipated when administered topically as discussed above.

Accordingly, reconsideration and withdrawal of all rejections under 35 U.S.C. § 103 are respectfully requested for claims 11-13, 16-26, and 33.

Claims 27-32 are rejected under 35 U.S.C. § 103 as being unpatentable over Yoji, Goodman, Elkhoury and Ptchelintsev as applied to claims 11-13, 16-26, and 33 above, and further in view of Mayer et al. (USPN 5,840,731 – "Mayer") Claims 34-35 are rejected under 35 U.S.C. § 103 as being unpatentable over Yoji, Goodman, Elkhoury and Ptchelintsev as applied to claims 11-13, 16-26, and 33 above, and further in view of Soo et al. (USPN 5,028,595 - Soo). Applicants respectfully disagree and traverse these rejections.

As stated above, the pending claims are directed to methods for providing synergistically effective amounts of morphine and butamben to potentiate analgesia at peripheral sites in a subject. As discussed in detail above, claims 11-13, 16-26, and 33 are nonobvious in view of the combination of cited references. Claims 27-32 and 34-35 ultimately depend from claim 11. If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Moreover, the further combination of either or Soo with the combination of Yoji, Goodman, Elkhoury and Ptchelintsev fails to teach or suggest topical synergism between morphine and butamben in the periphery. Accordingly, reconsideration and withdrawal of all rejections under 35 U.S.C. § 103 are respectfully requested for claims 27-32 and 34-35.

CONCLUSION

In view of the remarks made herein, the application is in condition for allowance. Favorable reconsideration and withdrawal of the rejections of the application, and prompt issuance of a Notice of Allowance are respectfully requested. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105.

Respectfully submitted,

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